IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Haim AVIV et al.

Confirmation No. 6729

Application No.: 10/644,687

Group Art Unit: 1626

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Examiner: Taofiq A. Solola

For: HIGH ENANTIOMERIC PURITY DEXANABINOL FOR PHARMACEUTICAL COMPOSITIONS

Attorney Docket No.: 87754-7500

DECLARATION OF AVIHAI YACOVAN

Commissioner for Patents
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Sir:

1. I am a citizen of Israel and currently reside at 10 Tzukerman Street, Gedera 70700, Israel.

2. I hold a Ph.D. Degree in Physical Organic Chemistry, received from Bar Ilan University, Ramat Gan, Israel, in 1995.

3. I am an employee of Pharmos Limited ("Pharmos"), an Israeli company having a place of business at Kiryat Weizmann, Rehovot 76326, Israel.

4. My present title at Pharmos is Director of Chemistry & Process Development and I have held this position for about a year and a half. I have worked in the Chemistry Department of Pharmos for about three years. I have ten years of experience in the research, synthesis, testing, and development of new compounds, compositions, and methods of making and using the same.

5. Pharmos no longer has any sample prepared as indicated by U.S. Patent No. 5,284,867 to Kloog et al. ("Kloog"). Thus, to obtain the closest comparable sample, a laboratory scale batch of HU-211 (dexanabinol) was prepared according to a slightly improved version of Mechoulam's original synthetic procedure ("Mechoulam sample"). This batch contains 91.1% HU-211 and 0.26% HU-210, which results in 99.4% enantiomeric excess. In

my opinion, these values represent the best values that could have been obtained by the original procedure followed by Kloog.

6. HU-211 was prepared on a large scale as clinical grade material according to the processes disclosed in the above-identified application, entitled "High Enantiomeric Purity Dexanabinol for Pharmaceutical Compositions", ("Ultrapure sample").

7. The Mechoulam and Ultrapure samples were tested for three of the four parameters usually measured in the mice tetrad assay. Suppression of spontaneous activity, hypothermia, and catalepsy were tested. The Mechoulam and Ultrapure samples were first dissolved in a mixture of 70% (w/w) CREMOPHORE EL® and 30% (w/w) ethanol and further diluted 1:20 in sterile saline. ICR male mice with an average body weight of 25 g (Harlan, Israel) were administered the Mechoulam or Ultrapure sample intravenously at a dose of 50 mg/kg and at a volume dose of 5 mL/kg. Untreated animals and animals injected with only the vehicle served as controls. Each group of animals included at least 5 mice.

Measurements were taken starting 15 minutes after administration of the samples. All tests were completed for each animal within about 5 minutes. Spontaneous locomotion was assessed using open field methodology. The number of squares crossed by the animals was recorded and analyzed during a 3-minute period. At the end of the open field test, the animals were tested for catalepsy symptoms for up to 1 minute. This was carried out by gently forcing the animal to stand on its hind paws with its front paws holding on to an elevated beam. The time it took for the animal to step down from the beam was measured in seconds. A normal animal withdraws from the beam immediately, whereas a cataleptic animal tends to stay on the beam. Finally, rectal temperature was monitored using a thermistor probe (YSI Model 400, USA). The results are expressed as an average ± SEM. The animals were euthanized at the end of the study.

8. The pattern displayed by the animals that served as controls was very similar in the three parameters tested, and their results were combined to establish baseline or normal values of untreated animals. The results for the animals treated with the Mechoulam or Ultrapure samples, compared to baseline or normal values, are shown in the table below.

Treatment	Rectal Temperature (°C)	Spontaneous Locomotion (No. of Squares)	Catalepsy (Sec)
Untreated (Control)	38.78 ± 0.18	74.51 ± 9.96	0.00 ± 0.00
Ultrapure	38.48 ± 0.12	86.58 ± 13.12	0.00 ± 0.00
Mechoulam	32.96 ± 0.25	4.42 ± 3.13	29.40 ± 8.69

9. The results in the table confirm that the Ultrapure sample has no adverse effect in mice at 50 mg/kg intravenously, whereas the Mechoulam sample clearly produces adverse effects. The Mechoulam sample causes a drastic drop in rectal temperature of about 6°C. The Mechoulam sample almost totally inhibited spontaneous locomotion, with the animals crossing only about 6% of the original number of squares they would normally traverse over the same period of time. Finally, the Mechoulam sample caused significant catalepsy, with the animals remaining immobile on the beam for almost 30 seconds.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, and any patent issuing thereon.

Dated: 8.9.05

Avihai Yacovan
Director of Chemistry & Process Development